

## THE PRESENT AND FUTURE

### STATE-OF-THE-ART REVIEW

# Left Ventricular Noncompaction

## A Distinct Cardiomyopathy or a Trait Shared by Different Cardiac Diseases?



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#### ABSTRACT

Whether left ventricular noncompaction (LVNC) is a distinct cardiomyopathy or a morphologic trait shared by different cardiomyopathies remains controversial. Current guidelines from professional organizations recommend different strategies for diagnosing and treating patients with LVNC. This state-of-the-art review discusses new insights into the basic mechanisms leading to LVNC, its clinical manifestations, treatment modalities, anatomy and pathology, embryology, genetics, epidemiology, and imaging. Three markers currently define LVNC: prominent left ventricular trabeculae, deep intertrabecular recesses, and a thin compacted layer. Although new genetic data from mice and humans supports LVNC as a distinct cardiomyopathy, evidence for LVNC as a shared morphological trait is not ruled out. Criteria supporting LVNC as a shared morphological trait may depend on consensus guidelines from the multiple professional organizations. Enhanced imaging and increased use of genetics are both predicted to significantly impact our overall understanding of the basic mechanisms causing LVNC and its optimal management. (J Am Coll Cardiol 2014;64:1840-50) © 2014 by the American College of Cardiology Foundation.

Left ventricular noncompaction (LVNC) is defined by 3 markers: prominent left ventricular (LV) trabeculae, deep intertrabecular recesses, and the thin compacted layer (1). The spectrum of morphologic variability is extreme, ranging from hearts with a nearly absent compacted layer and an almost exclusively trabecular component in the LV apex, to hearts with prominent trabeculae and deep alternating recesses, but a well-represented compacted layer. Whether LVNC is a distinct cardiomyopathy or a morphologic trait shared by different types of cardiomyopathies is still debated. LVNC can be isolated or associated with cardiomyopathies, congenital heart diseases,

and complex syndromes involving the heart. The American Heart Association classifies LVNC as a genetic cardiomyopathy (2), whereas the European Society of Cardiology classifies LVNC as an unclassified cardiomyopathy (3). The World Health Organization's International Classification of Diseases also reports LVNC as an unclassified cardiomyopathy. This state-of-the-art review includes data from embryology, genetic studies, epidemiology, and imaging studies (as outlined in a recent editorial on the evolution of translational medicine [4]), and provides an up-to-date view of current findings on the controversial topic of LVNC. Each of the authors selected published reports for

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this review on the basis of the most up-to-date criteria.

The LVNC trait may be familial (inherited) or nonfamilial (sporadic). Nonfamilial forms are diagnosed when LVNC is proven absent in relatives (5). Sporadic LVNC can be acquired, as in highly-trained athletes (6), sickle cell anemia patients (7), and pregnancy (8). In the pregnancy study by Gati et al. (8), 73% of affected women demonstrated complete resolution of the trabeculation during post-partum follow-up (8). In some cases, the trabeculation phenotype may occur in response to a mechanical load, and may disappear as the mechanical load dissipates. It is not known if there is a genetic underpinning to the disease in these cases (6-8). Cases in children suggest that 75% have electrocardiogram abnormalities, and most have depressed systolic function (9). Some children have transient recovery followed by later deterioration, suggesting that these cases in children are genetic in nature. The genetic bases of familial LVNC are still a matter of research. Most familial cases identified to date are associated with mutations in the same genes that cause other types of cardiomyopathies (10,11). Whether these disease genes cause the cardiomyopathy or the LVNC phenotype remains to be clarified (12). A limitation of many (but not all) of these genetic studies is that most only screened genes associated with other cardiomyopathies, such as sarcomeric genes, which are also associated with hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and dilated cardiomyopathy (DCM).

Although there is no current gold standard for LVNC diagnosis, cardiac imaging is the best tool currently available. Pathoanatomic investigation in autopsy hearts or in hearts excised at transplantation provides data for pathoimaging correlations and assessment of imaging-based diagnoses (13). The most commonly used imaging modalities include echocardiography and cardiac magnetic resonance (CMR). Echocardiography provides the basic tool for diagnosis (14), whereas CMR adds anatomic details and functional information on kinesis of the non-compacted versus compacted segments and fibrosis (15). The limitations of imaging will be discussed.

Clinical management is based on the functional phenotype and related complications. The management of atrial and ventricular arrhythmias, device implantation, resynchronization, ablation procedures, and even LV surgical remodeling has been a matter of specific attention, raising the question of whether LVNC deserves specific medical strategies (4,16).

## EMBRYOGENIC AND NONEMBRYOGENIC HYPOTHESES

There can be multiple etiologic bases of LVNC: it may occur as an isolated trait or disease (I-LVNC); in association with genetic diseases and congenital defects; be sporadic and acquired in physiological (6) or pathologic conditions (7); or be permanent or transient (8). Therefore, LVNC can originate during embryonic development or be acquired later in life.

**NONEMBRYOGENIC HYPOTHESIS.** Emerging evidence supports the hypothesis that the pathogenetic mechanisms leading to non-compaction or increased trabeculation may occur in adult life, leading to acquired LVNC. In young athletes, increased LV trabeculation may represent the effect of cardiac remodeling (6); in this case, trabeculation becomes more prominent, but the compacted layer is well represented. It has been suggested that “following ECG and echocardiography, 0.9% of highly trained athletes demonstrate concomitant T-wave inversion and reduced baseline indices of systolic function that may be considered diagnostic of LVNC” (6). The de novo LV trabeculations observed in a significant proportion (>25%) of pregnant women suggest that LV trabeculations may occur in response to increased LV loading conditions or other physiological adaptation mechanisms related to pregnancy (8). The increased trabeculation observed in individuals with sickle cell anemia may represent an exaggerated myocardial response to the increased cardiac pre-load (7). In summary, this evidence supports the hypothesis that particular phenotypic characteristics of LVNC are identified in cases including pregnancy, sickle cell anemia, and athletes.

**EMBRYOGENIC HYPOTHESIS.** Most data supporting the embryogenic hypothesis of LVNC come from experimental studies. Fetal echocardiographic studies may contribute to elucidation of the embryogenic mechanisms of LVNC and its association with other cardiac diseases. In a very elegant study by Arunamata et al. (17), 22 of 24 fetuses with LVNC had congenital heart disease, and 15 had complete heart block. Studies in identical twins may further expand the routes of investigation, especially when identical phenotypes are expected, but not observed (18).

Studies in experimental models suggest that the process of cardiac trabeculation begins after the cardiac looping stage. Trabeculae formation begins with the emergence of myocytes through delamination

## ABBREVIATIONS AND ACRONYMS

<b>ARVC</b>	= arrhythmogenic right ventricular cardiomyopathy
<b>CMR</b>	= cardiac magnetic resonance
<b>DCM</b>	= dilated cardiomyopathy
<b>FAK</b>	= focal adhesion kinase
<b>HCM</b>	= hypertrophic cardiomyopathy
<b>ICD</b>	= implantable cardioverter-defibrillator
<b>LV</b>	= left ventricle/ventricular
<b>LVNC</b>	= left ventricular noncompaction
<b>MIB1</b>	= mindbomb homolog 1 ( <i>Drosophila</i> )
<b>RCM</b>	= restrictive cardiomyopathy
<b>TAZ</b>	= tafazzin

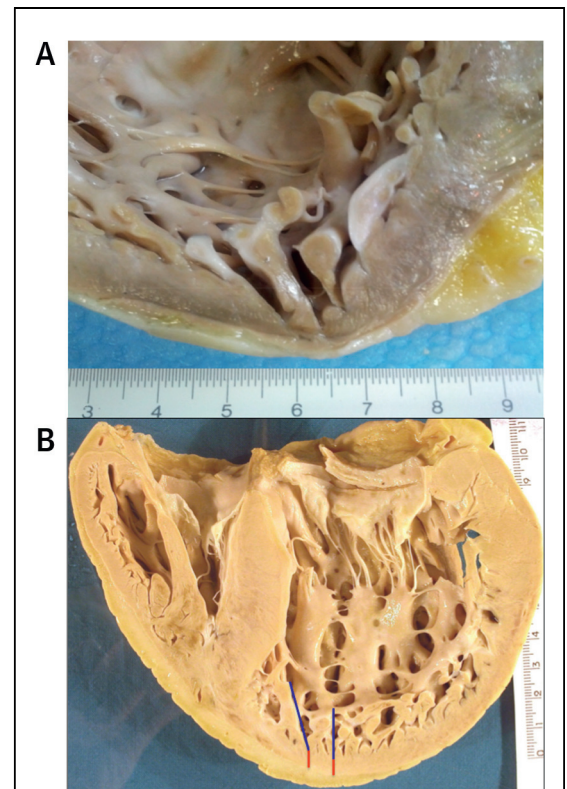
(migration) from the compacted myocardium (19). Emerging evidence suggests that the myocytes forming the trabeculae arise from a different clonal origin in the heart wall (19,20). Myocytes project radially into the cavity and are covered by the endocardial layer. This array guarantees the best perfusion of the myocytes by increasing the contact surface between the left ventricular cavity and the myocytes, while the coronary tree is not yet developed. Intertrabecular spaces are transformed into capillary vessels. Failure at this stage corresponds to the formation of thin elongated trabecular projections separated by deep recesses. The compact layers of myocytes proliferate, and the epicardium enters the myocardial wall and forms the coronary vasculature (21,22). Recent studies in zebrafish and mice suggest that cardiac trabeculation is mediated by endocardial neuregulin 1 through the ErbB4 and ErbB2 receptor complex (19,23-27). Deletion or mutation of the homologs of *Drosophila* mindbomb 1 (Mib1), Notch1, neuregulin 1, ErbB4, or *Erbb2* in zebrafish or mice results in the absence of trabecular formation. ErbB3 activation by Neuregulin 1 phosphorylates focal adhesion kinase (FAK). Systemic deletion of FAK in mice also results in a phenotype similar to LVNC (28,29). Thus, neuregulin 1 signaling through ErbB4 and ErbB2 leading to FAK phosphorylation appears integral to cardiac trabecular formation. Moreover, Notch signaling in the endocardium is also critical for cardiac trabecular formation (30,31).

As cardiac development progresses, myocytes compact by organizing into ordered bundles that progressively generate the compacted myocardial walls (more prominent in the left than in the right ventricle). The trabecular portion of the myocardial wall is tiny and thinner in the LV than in the right ventricle, and the compacted wall is more prominent in the thicker LV wall. Two embryologic morphogenetic hypotheses were formulated as potential explanations of LVNC pathogenesis. Hypothesis 1 states that arrested or abnormal myocardial morphogenesis leading to LVNC occurs during heart development, when myocyte organization fails to evolve from the embryonic spongiform condition to the compacted, mature state. Although both ventricles may be involved, the LV is generally affected (32). Hypothesis 2 states that LVNC occurs as a result of inhibiting the regression of embryonic structures (33). Sponginess would result from the looseness of cells or of cell bundles. LVNC describes a macroscopic mismatch between the noncompacted trabeculae and the compacted myocyte layers. Myocytes in the trabeculae do not show histologic differences from those forming the compacted layer, which explains why LVNC

histology (i.e., endomyocardial biopsy) does not specifically contribute to the diagnosis. The diagnostic hallmark of LVNC is the macroscopic appearance that correlates with imaging findings.

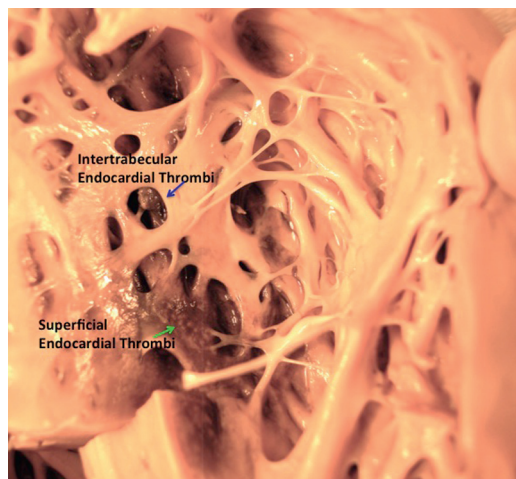
## ANATOMY AND PATHOLOGY

In hearts excised at transplantation or at autopsy, LVNC diagnosis is on the basis of the prominent appearance of LV trabeculae and the ratio between the compacted and noncompacted LV wall (13). Sectioning of formalin-fixed hearts provides the best way of measuring compacted and noncompacted layers (34). Prominent trabeculae and thin, compacted myocardial layers can be described either



**FIGURE 1** Two Hearts Depicting the Variability in Both Extension and Depth of Trabeculae and Recesses

(A) In this high-magnification view of the apical wall of the heart, the noncompacted area is limited to a few apical trabeculae. The patient harbored mutations p.(Arg495Trp) in *myosin binding protein cardiac 3* (*MYBPC3*) and p.(Asp117Asn) in *Lim domain binding protein 3* (*LDB3*) genes ( $M_{H+D}$  O<sub>H</sub> G<sub>AD</sub> E<sub>G</sub>-*MYBPC3* [p.Arg495Trp]+*LDB3* [p.Asp117Asn]<sup>SC-IV</sup>). Although *LDB3* is a candidate gene for LVNC, in this family, the disease segregated with the mutation in *MYBPC3*. (B) In this heart, the prominent trabeculations (blue line) and deep recesses (red line) involve the entire left ventricular apex.



**FIGURE 2** High-Magnification View of Intertrabecular and Endocardial Thrombotic Stratification

Intertrabecular thrombotic stratification is indicated by a blue arrow, and endocardial thrombotic stratification by a green arrow.

as suggestive of LVNC or as increased trabeculation when the noncompacted/compacted ratio does not meet that commonly used (2.3) in imaging diagnosis (35). The pathologic diagnosis should not be forced into imaging criteria, but should provide data for a pathology-imaging correlation (Figure 1). Imaging is especially useful for identifying mural thrombi wedged within the intertrabecular recesses (especially common in hypokinetic LVs) (Figure 2).

LV dilation and LV hypertrophy can be present or absent and do not influence LVNC diagnosis. Given the common localization of the noncompacted areas in the apex and the common localization on LV hypertrophy at the septum, the 2 diagnoses of HCM and LVNC can coexist. The topographic distribution of LVNC does not typically extend to the interventricular septum, although the septum may be involved in rare cases. LVNC has also been described in association with RCM. In pure RCM, the enlarged atria and the small nonhypertrophic ventricles support the pathologic diagnosis. The “restriction” is a functional diagnostic clue that can be inferred in pathologic studies by the atrial/ventricular size mismatch in the absence of significant LV hypertrophy. LVNC may also coexist with arrhythmogenic right ventricular cardiomyopathy (ARVC). In classical ARVC without involvement of the LV, the presence of LVNC is independent of the right side cardiomyopathy. In this context, the causes of ARVC and LVNC may not coincide. In biventricular and predominantly left

arrhythmogenic cardiomyopathies, the presence of LVNC may be considered either as an independent trait or as part of the arrhythmogenic cardiomyopathy involving the LV. The pathology study should contribute to characterization of LVNC as an isolated finding or as a trait present in cardiomyopathy in autopsied hearts and in hearts excised at transplantation. Finally, fibrous endocardial thickening can be present; it may reflect the effect of volume overload in LVNC in DCM or the organization pattern of mural thrombi. Overall, LVNC can be observed in all types of cardiomyopathies.

## EPIDEMIOLOGY

LVNC occurs in infants (0.81 per 100,000 infants/year), children (0.12 cases per 100,000 children/year) (21), and adults (prevalence 0.014%) (33). It can occur as an isolated myocardial trait or be associated with cardiomyopathies (hypertrophic, restrictive, dilated, and arrhythmogenic), congenital heart diseases (36), and complex syndromes affecting multiple organs and tissues, including mitochondrial diseases caused by mutations in both nuclear (23) and mitochondrial genes (24). In isolated LVNC, the intertrabecular recesses communicate with the LV cavity. LVNC was first described in 1984, in Engberding and Bender’s (37) description of the first echocardiographic diagnosis of persistence of isolated myocardial sinusoids. In patients with LVNC associated with other congenital heart diseases, the deep intertrabecular recesses communicate with both the LV cavity and the coronary circulation (33). LVNC was first described by Bellet and Gouley (38) in 1932, when they observed abnormally “spongy” myocardial walls associated with aortic atresia and coronary-ventricular fistula in an autopsy of a newborn with congenital heart disease.

By itself, “LVNC” does not necessarily describe a disease; it describes an anatomic variant of LV structure (39,40). There is wide variability in the ratio between trabeculated and compacted layers of the LV. At 1 extreme, severe forms of LV apex non-compaction and inferior/lateral walls are typically seen in children with Barth syndrome. In these patients, LVNC is associated with LV dilation and dysfunction (41). At the other extreme, hypertrabeculation with prominent (but less pronounced) trabeculations and intertrabecular recesses associated with a preserved, compacted layer is more common. Ethnic differences in the amount of trabeculation have been observed; Gati et al. (6) suggested prominent LV trabeculation was more prevalent in African-American subjects.



TABLE 1 Genes Associated With LVNC							
Location	Phenotype	Phenotype MIM Number	Gene/Locus	Gene/Locus MIM Number	Additional Phenotypes	Mode of Inheritance	Ref. #
1p36.32	Left ventricular noncompaction 8	615373	PRDM16	605557	Dilated cardiomyopathy	Autosomal dominant	(77)
1q32.1	Left ventricular noncompaction 6	601494	TNNT2	191045	Dilated cardiomyopathy	Autosomal dominant	(78)
10q23.2	Left ventricular noncompaction 3	601493	LDB3	605906	Dilated cardiomyopathy	Autosomal dominant	(79)
11p15	Left ventricular noncompaction 2	609470	None	609470	—	Autosomal dominant	(80)
11p11.2	Left ventricular noncompaction 10	615396	MYBPC3	600958	Dilated cardiomyopathy	Autosomal dominant	(81)
14q11.2	Left ventricular noncompaction 5	613426	MYH7	160760	Dilated cardiomyopathy	Autosomal dominant	(80,82)
15q14	Left ventricular noncompaction 4	613424	ACTC1	102540	Dilated cardiomyopathy	Autosomal dominant	(83)
15q22.2	Left ventricular noncompaction 9	611878	TPM1	191010	Dilated cardiomyopathy	—	(81)
18q11.2	Left ventricular noncompaction 7	615092	MIB1	608677	—	Autosomal dominant	(30)
18q12.1	Left ventricular noncompaction 1	604169	DTNA	601239	With or without congenital heart defects	Autosomal dominant	(84)
Xq28	Barth syndrome	302060	G4.5, TAZ	300394	Failure to thrive Failure to grow	X-linked recessive	(71)
<p>This table was adapted from Online Mendelian Inheritance in Man (OMIM). Additional information is available at the OMIM website (85). From left to right, the table provides the location for each locus, the phenotype (with a number that refers to phenotypes associated with the particular genes or loci), the phenotype MIM number, gene/locus, the gene/locus MIM number, additional phenotypes, mode of inheritance, and references. MIM number refers to a numerical assignment for genes and functional segments of deoxyribonucleic acid, as well as to inherited diseases. X-linked recessive indicates that both matching genes must be abnormal to cause the disease.</p> <p>ACTC1 = actin, alpha, cardiac muscle; DTNA = dystrobrevin alpha; LDB3 = Lim domain-binding 3; LVNC = left ventricular noncompaction; MIB1 = homolog of <i>Drosophila</i> mindbomb; MYBPC3 = myosin-binding protein C, cardiac; MYH7 = myosin heavy chain 7, cardiac muscle, beta; PRDM16 = PR domain-containing protein 16; TAZ = tafazzin; TNNT2 = troponin T2; TPM1 = tropomyosin 1.</p>							

## GENETICS

This paper’s title posed the question of whether LVNC is a “distinct cardiomyopathy or a trait shared by different cardiac diseases.” Human genetic studies suggest that several genes are associated with LVNC (Table 1).

Nearly all of the genes associated with LVNC are associated with additional phenotypes, like cardiomyopathies or congenital heart defects. However, mutations in 1 gene, MIB1, segregated with autosomal dominant LVNC in 2 Spanish families, and a conditional loss-of-function allele in a mouse also led to LVNC (30). The hypertrabeculation and noncompaction seen in the Mib1 mouse was mimicked in a mouse with inactivation of Jagged1 in the myocardium or Notch1 in the endocardium, suggesting that the Notch1 signaling pathway was, indeed, involved (30). Chen et al. (31) recently reported an important role in trabeculation for endocardial expression of a Notch ligand, Fkbp1a. These findings firmly support the hypothesis that in some circumstances, LVNC is a cardiomyopathy, and dysregulated Notch signaling in the endocardium leads to disrupted trabeculation.

Barth syndrome is an X-linked recessive disorder that is diagnosed either pre-natally or in infants and is characterized by failure to thrive, growth retardation,

and cardiovascular abnormalities including LVNC (5,42). It is probably 1 of the few cardiomyopathies that can be pre-natally recognized with imaging (42), and typically includes hypokinetic DCM with LVNC that can cause death in early infancy. Barth syndrome is associated with the gene G4.5, encoding tafazzin (TAZ), a mitochondrial protein critical for remodeling of the phospholipid, cardiolipin. TAZ knockdown mice die embryonically with cardiomyopathy characterized by hypertrabeculation and noncompaction (43). The mouse model together with human TAZ and Barth syndrome data provide additional evidence that genetic pathways can lead directly to hypertrabeculation and noncompaction, suggesting that in some instances, LVNC is a cardiomyopathy (30,44).

Other LVNC-associated genes in Table 1 are also associated with additional phenotypes, including cardiomyopathies (45). LVNC lacks genome-wide association studies for LVNC, which would be challenging, given that patients present with pleiotropic phenotypes (46). Additional limitations include that most studies reported to date are underpowered, limiting their strength. Although whole-genome and -exome sequencing permit the discovery of a new complexity of genotypes (46), many studies reported to date do not report clinical whole-genome or -exome sequencing, but instead sequence candidate

DIAGNOSIS	MONITORING	TREATMENT
<p>Echocardiographic diagnosis of LVNC in probands</p> <p>Cardiac magnetic resonance (CMR) (confirms the diagnosis, adds information)</p> <p>Family history and echocardiographic screening of relatives (helpful for confirming diagnosis in family members and/or determining potential development in family members)</p> <p>Genetic testing in probands:</p> <ul style="list-style-type: none"> <li>• Clinically guided in case of suspected syndromes/diseases typically showing LVNC (ie. Barth Syndrome)</li> <li>• Testing for genes known to be associated with LVNC</li> </ul> <p>in relatives:</p> <ul style="list-style-type: none"> <li>• Cascade genetic testing in relatives, after identification of mutation in the proband</li> <li>• Segregation studies in the family</li> </ul>	<p>Clinical monitoring in probands:</p> <ul style="list-style-type: none"> <li>• Physical exam</li> <li>• Electrocardiogram</li> <li>• Echocardiogram</li> <li>• CK-MM (creatinine kinase-MM isoform) (at initial evaluation only)</li> </ul> <p>in first degree relatives of LVNC patients:</p> <p>Clinical screening every 3 years beginning in childhood</p> <p>If a mutation is identified, clinical screening is recommended yearly in childhood and every 1-3 years in adults</p>	<p>Depending on the phenotype, patients are managed according to their clinical needs and corresponding guidelines</p> <p>Oral anticoagulation medicine</p> <p>Cardioverter defibrillator (ICD) implantation</p> <p>Cardiac resynchronization therapy</p>

#### CENTRAL ILLUSTRATION A Clinical Management Outline for LVNC

Diagnosis and screening strategies for probands and relatives are listed in the **left panel**, clinical monitoring guides are listed in the **middle panel**, and treatment options are outlined in the **right panel**. Data for this table was selected from the Online Mendelian Inheritance in Man (85), established as a collaboration between the Institute of Genetic Medicine, Johns Hopkins Medicine, and the National Human Genome Research Institute. ICD = implantable cardioverter-defibrillator; LVNC = left ventricular noncompaction.

genes. Pairing new complex genotypes with complex phenotypes like LVNC requires criteria for phenotyping and quality control for genotyping. Thus, at this early stage, we cannot rule out modifier genes or the potential for several genes to influence the LVNC phenotype. Epigenetic (i.e., deoxyribonucleic acid methylation) or environmental causes, such as increased mechanical load or stress that may induce the phenotype, are additional possibilities. A recent study using high-resolution episcopic microscopy and 3-dimensional reconstruction shows (with high sensitivity and quantification) hypertrabeculation in the Mib1 loss-of-function allele mouse, compared with a wild-type mouse (47).

The **Central Illustration** outlines LVNC management. In the left panel, under diagnosis, we suggest imaging for the initial diagnostic tool in the proband. To confirm diagnosis or determine potential involvement in family members, family history and echocardiographic screening are 2 potential options. In cases of suspected syndromes, such as Barth syndrome (an X-linked recessive disorder), genetic testing in probands is suggested, given the relatively high fatality rate. Genetic testing in relatives is an additional option after the mutation in the proband is identified.

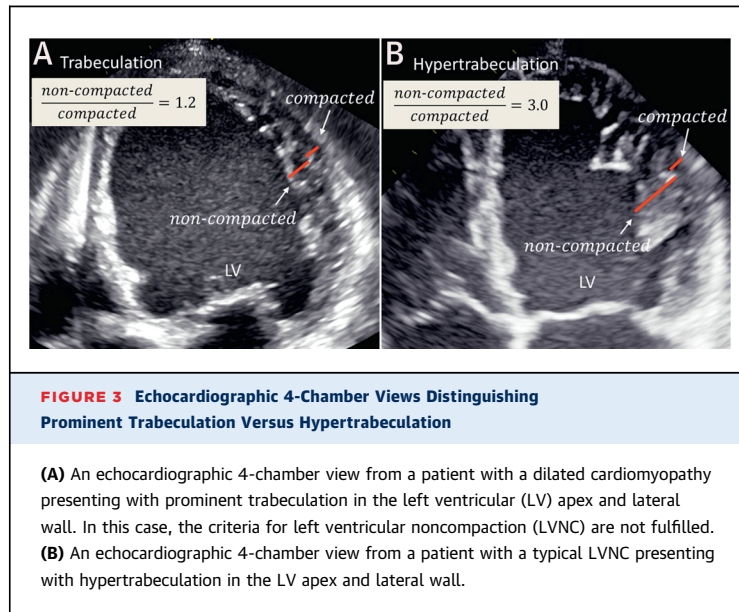
Clinical monitoring options in probands (**Central Illustration**, middle panel) include physical examination, electrocardiogram, echocardiogram, and creatine kinase MM isoform. For monitoring of first-

degree relatives, options include clinical screening every 3 years beginning in childhood and, if a mutation is identified, annual clinical screening in children and every 1 to 3 years in adults.

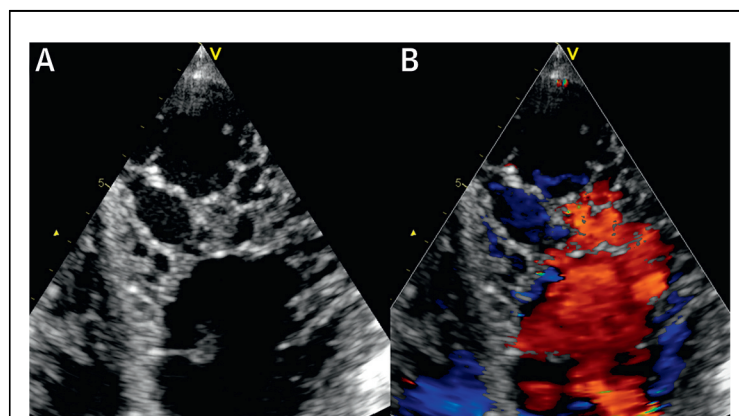
Treatment and management options are listed in the far right panel of the **Central Illustration** and depend entirely on the patient's phenotype and clinical needs and the corresponding guidelines (see Management section). Three topics will be touched on: oral anticoagulation medicine, cardioverter-defibrillator implantation, and cardiac resynchronization.

#### IMAGING AND DIAGNOSIS

**ECHOCARDIOGRAPHY.** Standard echocardiography is the first diagnostic tool for LVNC in both index patients and family members. Two-dimensional grayscale echocardiography is the most common and useful tool for LVNC diagnosis, showing both broad trabeculae and deep intertrabecular recesses in the LV myocardium, typically located in the LV apex and the midinferior and lateral walls. In contrast, the basal and midinterventricular septum scanned by an apical 4-chamber view is typically free of trabeculae (**Figure 3**). In most patients, it is necessary to image the LV not only with standard defined imaging views, but also with atypical views to image the more apical segments of the LV and detect the prominent trabeculae (**Figure 4**).



Several echocardiographic diagnostic criteria for isolated LVNC are available (48-51), but none can be considered the gold standard for LVNC diagnosis. Furthermore, the criteria are indirect, assessing morphological abnormalities. After careful evaluation of all criteria, the most important echocardiographic criterion remains a noncompacted/compacted ratio  $>2.0$  in end-systole (49,50). However, when using this ratio to diagnose LVNC, one must keep its quite high interobserver and intraobserver variability in mind as a limitation. Importantly, for LVNC diagnosis, the aforementioned imaging criteria may be considered together with family history and genetics.



In addition to morphological abnormalities, systolic dysfunction is frequently present in LVNC hearts. It was hypothesized that small vessel “dysfunction” with impaired coronary flow reserve and microcirculatory defects, together with a primary myocardial disease, is responsible for the functional abnormalities (52). Thus, in classical LVNC cases, especially in advanced stages, both hypokinetic and akinetic regions can be detected in the diseased segments by wall motion analysis. Recent studies suggest that deformation imaging could better reveal systolic impairment in patients with LVNC, even in those with preserved LV ejection fraction (53,54). In addition, a tissue Doppler-derived strain rate study demonstrated a distinct deformation pattern in LVNC, with significantly higher longitudinal systolic strain rate and strain in the basal segments than in the apex, which could help differentiate LVNC from DCM (55).

Diastolic dysfunction is another typical echocardiographic feature of LVNC. Thus, most patients (even children) present with abnormal diastolic filling parameters (56). Diastolic dysfunction is attributed in part to abnormal relaxation resulting from extensive trabeculation (57).

**CONTRAST ECHOCARDIOGRAPHY.** In obese patients or patients with lung disease who may have poor acoustic windows, conventional echocardiography has diagnostic limitations. In these cases, the diagnosis is often missed because of imaging quality limitations, especially in the more apical region of the heart. Echocardiographic contrast imaging with various contrast agents enhances endocardial border definition and could improve detection of this rare cardiomyopathy, which could otherwise be misdiagnosed (58,59). Thus, when conventional echocardiographic images are poor or diagnosis is uncertain, contrast echocardiography can be helpful.

**CARDIAC MAGNETIC RESONANCE.** CMR may help to accurately describe and diagnose LVNC and distinguish true LVNC from the prominent hypertrabeculation that can be seen in normal hearts and individuals (Figure 5) (60). The major advantage of CMR is that a 3-dimensional dataset with equal image quality can be acquired. Thus, potential trabeculae at any region cannot be missed. The major marker is (as for echocardiography) the presence of several prominent trabeculations in the LV with topographic involvement of apical and mid segments of the lateral and inferior walls. Prior studies were performed in small clinical series (61,62). A noncompacted/compacted ratio  $>2.3$  on CMR is considered the cutoff for LVNC diagnosis (Figure 6) (61). This criterion yielded  $>43\%$  of positive subjects in MESA

(Multi-Ethnic Study of Atherosclerosis) (39). Importantly, to avoid misdiagnosis, compact papillary muscle should be distinguished from prominent trabeculations, which is quite easy to do with the 3-dimensional dataset acquired during CMR.

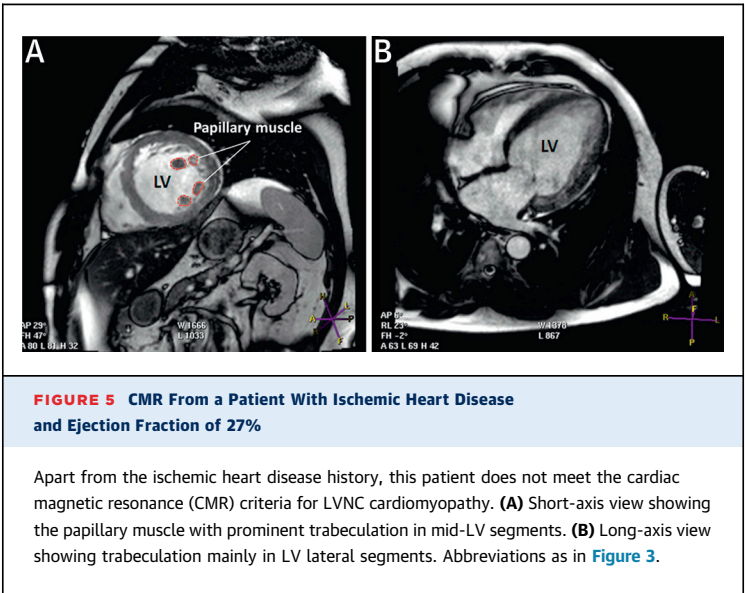
Fractal analysis was also used to quantify LV trabeculae (15). In a recent study of 30 patients, the combination of end-diastolic measurements at basal, mid, and apical segments was found to be the best selector of LVNC cases from the normal population (63). When grouping patients according to normal and reduced ejection fraction, interpretation of the data was challenged by the unanswered question of whether normal and low ejection fraction groups simply represent 2 phases of the same condition diagnosed at different evolutionary stages, or whether they represent the phenotypes of different diseases. The authors concluded that “A gold standard for the diagnosis of LVNC continues to be lacking as no imaging or pathology signature has yet been agreed” (64). While waiting for the ideal definition and diagnostic criteria, a descriptive diagnosis including both LVNC and the LV morphofunctional phenotype (e.g., DCM-like, HCM-like) can be adopted to collect data from emerging series.

The typical 2-layered structure of the LV wall can be better measured in CMR, where the thinner, compacted layer can be precisely measured in affected ventricular segments. As in echocardiography, functional data (hypokinesis of the noncompacted segments vs. normal kinesis of unaffected segments) may further strengthen the diagnostic hypothesis.

Advanced CMR modalities can provide additional information. For example, high-intensity endocardial T2 signals, subendocardial perfusion defects, and delayed enhancement of the subendocardial layer can add information about function and fibrosis of the affected segments and the possibility of assessing whether abnormalities coincide with noncompacted versus compacted segments (65,66). Advances in imaging are contributing to the ability to distinguish pathologic LVNC from nonpathologic hypertrabeculation. The correct diagnosis may prevent unneeded restrictions for athletes (61). A current gap is the inability to establish the thickness and functionality of the thin, compacted LVNC heart layers. This knowledge may lead to improved clinical management.

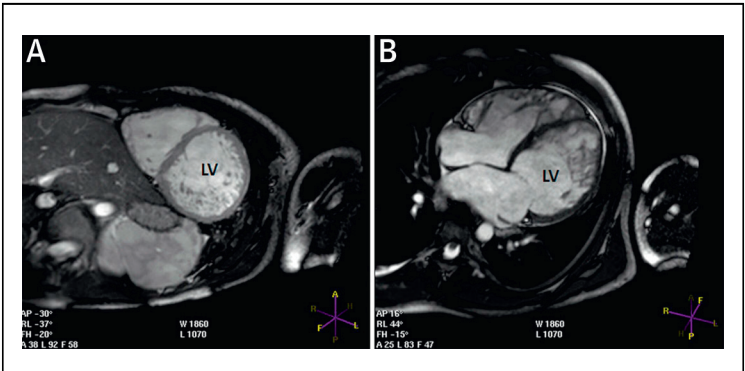
## MANAGEMENT OF LVNC

There are no specific guidelines for management of LVNC. Management includes confirmation of the echocardiographic or CMR diagnosis. Differential diagnoses include prominent hypertrabeculation



with normal compacted LV layer, apical HCM, DCM, endocardial fibroelastosis, and LV apical thrombus.

Clinical management of LVNC depends on the presence or absence of cardiac dysfunction or arrhythmias. Patients with normal LV size and function undergo clinical monitoring, whereas symptomatic patients with LV dilation and dysfunction or hypertrophy may be clinically managed according to phenotype. Guidelines suggest that familial LVNC should be diagnosed by echocardiographic screening of family members (45). Echocardiographic screening is recommended for family members, given that the symptoms are variable and the risks include heart failure and sudden cardiac death. Genetic testing for LVNC does not change clinical management of the





disease; however, it may be helpful for confirming diagnoses in family members and/or determining potential development in family members to aid in the timing of screening (**Central Illustration**) (67).

Clinical monitoring may include clinical history, physical examination, echocardiography, Holter monitoring, and measurement of high-sensitivity troponin (**Central Illustration**).

Currently, there are no specific treatments for LVNC. Depending on the phenotype, patients are managed according to their clinical needs and corresponding guidelines (e.g., for congestive heart failure, arrhythmias). Oral anticoagulation is a debated issue in subjects with normal LV function and absence of LV hypertrophy: patients are either treated on the basis of the phenotype (oral anticoagulation given independently on arrhythmias or LV dysfunction for primary prevention of embolic episodes) or in the presence of LV dysfunction, arrhythmias, prior embolic events, or proven atrial or ventricular thrombi.

Complications with LVNC include heart failure, arrhythmias including sudden cardiac death, and systemic embolic events (16). Atrial tachycardia and fibrillation are common. Ventricular tachyarrhythmias have been reported in up to 47% of symptomatic patients referred to a tertiary referral center, and SCD has been reported in 13% to 18% of (mostly adult) patients with LVNC. Whether the risk of ventricular arrhythmias is higher than that seen in patients with corresponding functional phenotypes (DCM, HCM, and so forth) is not clear. As anticipated (68), LVNC has been considered a reason to restrict athletic participation (33,69,70). However, a 48.6 ± 14.6-month follow-up in athletes fulfilling LVNC criteria did not reveal adverse events (6), thus caution is advised before introducing restrictions based on isolated LVNC.

It is unknown whether or not the small compacted layer and the deep recesses of the heart in patients with LVNC increases the risk of complications, such as ventricular perforation in interventional occasions or implantation of devices. This issue is not governed by guidelines, and decisions may be eventually supported by tailored evaluations of families, including evidence of sudden death in affected relatives. In 30 patients with LVNC who underwent implantable cardioverter-defibrillator (ICD) insertion for secondary or primary prevention, 11 patients (37%) had appropriate ICD therapies in a mean follow-up period of 40 ± 34 months: 3 with antitachycardia pacing, 4 with ICD shocks, and 4 with both antitachycardia pacing and ICD shocks (69). Although clinical predictors for appropriate ICD therapy are not available,

this single study suggests that ICD therapy may be effective in patients with LVNC. Cardiac resynchronization therapy improves New York Heart Association functional class in patients with LVNC and may hence be considered in patients with an LV ejection fraction ≤35% and signs of ventricular dyssynchrony (71,72). More studies need to be completed to determine the safety and efficacy of the use of ICDs in patients with LVNC.

## SUMMARY AND CONCLUSIONS

In summary, evidence that LVNC is a cardiomyopathy includes the following: 1) specific mutations in genes in the Notch1 pathway in mice and humans leading to dysregulated signaling and hypertrabeculation and noncompaction; and 2) specific mutations in G4.5 in mice and humans disrupting the TAZ protein leading to dysregulated remodeling of cardiolipin and Barth syndrome, characterized by hypertrabeculation and noncompaction in utero and failure to thrive. In contrast, evidence that LVNC is a trait shared by multiple cardiac diseases has not been ruled out. The data presented on mechanical load from pregnancy and athletes is compelling. However, Notch1 signaling is involved in mechanosensation (73–75), suggesting that individuals who develop LVNC may have an underlying mutation in a gene that disrupts Notch signaling or in other endocardially-expressed mechanosensing genes. In these patients, an additional modifier, such as stress or increased load, may be needed for the phenotype to present.

Although echocardiography and CMR are useful for LVNC diagnosis, these approaches are indirect and present limitations of interobserver and intra-observer variability. Guidelines for clinical management of LVNC suggest that familial LVNC should be diagnosed by echocardiographic screening of family members. Genetic testing does not change clinical management of the disease, but may be helpful for confirming diagnosis in family members and/or determining potential development in family members to aid in the timing of screening. Anticoagulation is the only medication that can be administered in addition to therapies commonly used in phenotype-based management of cardiomyopathies. We suggest that the American Heart Association, World Health Organization, and the European Society of Cardiology form a working group in the near future, and agree on guidelines to specifically define:

1. LVNC as primary pathology, which can be isolated or associated with cardiomyopathy. It may be

clinically useful to indicate the cardiomyopathy phenotype and the LVNC (HCM-LVNC, RCM-LVNC, DCM-LVNC, or ARVC-LVNC) to distinguish I-LVNC with normal LV size and function.

2. The role of LVNC as a marker for addressing clinical and genetic diagnostic hypotheses.
3. Reproducible and unified imaging-based diagnostic criteria for LVNC.
4. The risk of thrombosis in patients with I-LVNC, especially when LV size and function are normal.

In parallel, to establish real-world data and outcomes in LVNC patients, we recommend increased collection of LVNC electronic health record data, with imaging data and genetic information, if possible (76).

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